IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	Confirmation No. 9946
ZLOKOVIC	Atty. Ref.: 4061-28
Appln. No. 10/516,729	T.C. / Art Unit: 1647
Filed: December 6, 2004	Examiner: D.E. Kolker

FOR: TREATMENT OF VASCULAR DYSFUNCTION AND ALZHEIMER'S DISEASE

* * *

BRIEF FOR APPEAL UNDER 37 CFR § 41.37

June 23, 2009

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant submits this Brief to appeal the Examiner's final rejection as set forth in his Office Action mailed December 12, 2007, (the "final Office Action"). The fee required under 37 CFR § 41.20(b)(2) was previously submitted.

The Notification of Non-Compliant Appeal Brief was mailed May 27, 2009 and set a one-month period for response. Therefore, this Brief is timely filed.

Reversal of the Examiner's rejection of claims 1-2, 5-6 and 27-40 by the Board of Patent Appeals and Interferences (the "Board") is respectfully requested.

I. REAL PARTY IN INTEREST

The assignees, The University of Rochester and Socratech L.L.C., hold all rights in the subject invention, as well as the invention disclosed and claimed therein, by the

assignment recorded on March 2, 2005 in the Patent and Trademark Office starting at reel 016322 and frame 0639.

II. RELATED APPEALS AND INTERFERENCES

Appellant, the assignees, and the undersigned do not know of any prior or pending appeal, interference, or judicial proceeding which is related to, directly affects or is directly affected by, or has a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 1-2, 5-6 and 27-40 stand rejected. They are at issue in this appeal and listed in the Claims Appendix.

Claims 7-26 were withdrawn from consideration by the Examiner as directed to nonelected inventions.

Claims 3-4 and 7-26 were canceled without prejudice or disclaimer.

IV. STATUS OF AMENDMENTS

An after-final Amendment was submitted on June 12, 2008. In response thereto, the Examiner stated in his Advisory Action mailed July 2, 2008 that these amendments would be entered and that they overcome the Section 102 rejections.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 is directed to methods of assaying for vascular dysfunction in a human subject affected by a neurodegenerative disorder or another cognitive impairment by

determining whether there is inappropriate senescence and/or defective angio-genesis in endothelial cells of the human subject. The obtaining endothelium and endothelial cells from the subject, and their culture prior to assay, are supported by the specification at page 12, lines 21-28. Correlating dysregulated vascular function with inappropriate senescence and/or defective angiogenesis is supported by the specification at page 10, lines 5-21. Neurodegenerative disorders and cognitive impairments are described in the specification at page 29, lines 1-6.

Claim 27 is directed to methods of assaying for vascular dysfunction in a human subject affected by a neurodegenerative disorder or another cognitive impairment by determining whether there is inappropriate senescence and/or defective angiogenesis in endothelial cells of the human subject. The obtaining endothelium and endothelial cells from the subject, and their culture prior to assay, are supported by the specification at page 12, lines 21-28. Correlating dysregulated vascular function with inappropriate senescence and/or defective angiogenesis is supported by the specification at page 10, lines 5-21. Neurodegenerative disorders and cognitive impairments are described in the specification at page 29, lines 1-6.

Claim 33 is directed to the specific embodiment in which the human subject is affected by Alzheimer's disease. See original claim 2.

Claim 39 is directed to the specific embodiment in which defective angiogenesis is determined. See original claim 6. Cell culture prior to determining whether there is defective angiogenesis is not necessarily required. See original claim 1.

Support for each independent claims (i.e., claims 1, 27, 33 and 39) is provided. No dependent claim is argued separately.

Therefore, the invention as presently claimed is clearly supported by Appellant's disclosure as originally filed.

VI. GROUND OF REJECTION TO BE REVIEWED ON APPEAL

Under 35 U.S.C. 103, was it proper to reject claims 1-2, 5-6 and 27-40 as allegedly being unpatentable over Grammas et al. (Dementia 6:126-130, 1995) in view of Mulliken (Surgery 92:348-353, 1982)?

In his Advisory Action, the Examiner stated the after-final amendments would be entered and they overcome the rejections under 35 U.S.C. 102. Thus, the only ground for rejection to be reviewed by the Board is whether the present claims are obvious over the cited documents.

VII. ARGUMENTS

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by

the patent at issue"). The use of hindsight reasoning is impermissible. See id. At 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1396. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

35 U.S.C. 103 – Nonobviousness

Claims 1-2, 5-6 and 27-40 stand or fall together. The claims were rejected under Section 103(a) as allegedly being unpatentable over Grammas et al. (Dementia 6:126-130, 1995) in view of Mulliken (Surgery 92:348-353, 1982). Appellant traverses.

Grammas discloses the effects of amyloid fractions from an Alzheimer disease patient's brain on normal endothelial cells cultured from rat brains. The cited document focuses on the popular hypothesis that amyloid protein is responsible for the pathology seen in Alzheimer's disease instead of the discovery disclosed in Appellant's specification, which is based on endothelial cells having one or more intrinsic defects that would be the cause of vascular dysfunction in a human subject affected by a neurodegenerative disorder or another cognitive impairment. In neither Grammas nor Mulliken are

dysfunctional cells from a human subject assayed directly or after culturing for vascular dysfunction.

Grammas cultures normal endothelial cells from rat brains. As admitted in the Office Action at page 5, "Mulliken does not teach obtaining endothelial tissue from patients with neurodegenerative disease or another cognitive impairments" (emphasis added). Therefore, neither of the cited documents discloses culturing endothelium or endothelial cells from a diseased subject. Even if the disclosures of Grammas and Mulliken were combined as proposed by the Examiner in his Office Action, the combination would not render obvious determining whether there is inappropriate senescence and/or defective angiogenesis in endothelial cells from a human subject affected by a neurodegenerative disorder or another cognitive impairment as indicative of vascular dysfunction. This was a surprising result when the invention was made. An inquiry is required as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* 82 USPQ2d at 1396. But there was no inquiry by the Examiner as required for an obviousness rejection.

Even assuming for the sake of argument that "[i]t would have been obvious to one of ordinary skill in the art to modify the methods of Grammas to include the step of culturing the human endothelial cells, as taught by Mullliken, with a reasonable expectation of success" (the Office Action at page 5), the modification asserted by the Examiner would not result in Appellant's claimed invention. Here, Appellant's claimed methods assay for vascular dysfunction in endothelium or endothelial cells obtained from a human subject affected by a neurodegenerative disorder or another cognitive impairment (e.g., Alzheimer's disease). There would have been no reason to assay endothe-

lium or endothelial cells for vascular dysfunction because the cited documents focus on toxic effects of Aβ peptide (i.e., an extrinsic effect on cells) instead of Appellant's focus on intrinsic endothelial cell dysfunction. In contrast, the prior art would have used endothelium or endothelial cells from a normal human subject to avoid having to separate the effects of Aβ peptide on the cell in a subject affected by Alzheimer's disease *before* and *after* it was obtained from the subject. For this reason, both Grammas and Mulliken (and other prior art) teach culturing normal cells from a subject who is not affected by disease instead of from an affected subject as required by the present claims.

A reasonable expectation of success is also lacking because the prior art does not establish that the defect in Alzheimer's disease is intrinsic to the endothelium or endothelial cells of an affected subject. The popular hypothesis taught by Grammas is that the defect is centered on Aβ peptide that is extrinsic to cells. Therefore, extrinsic effects of the Aβ peptide on normal cells are assayed in the prior art.

Appellant submits that these features of his claimed invention are sufficient to distinguish over the cited documents so any other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Therefore, the combination of Grammas and Mulliken does not render obvious the claimed invention because all limitations of the independent claims are not fairly taught or rendered obvious by the cited documents. Moreover, claims depending from those independent claims are also not made obvious by the documents because their limitations are incorporated in the dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Appellant urges reversal of the Examiner's Section 103 rejection by the Board because the presently claimed invention would not have been obvious to one of ordinary skill in the art at the time it was made.

Conclusion

For the reasons discussed above, the Examiner's rejection is improper and it should be reversed by the Board. Appellant submits that the present claims are in condition for allowance and earnestly solicit an early Notice to that effect.

Respectfully submitted,

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VIII. CLAIMS APPENDIX

1. A method of assaying for vascular dysfunction in a human subject affected by a neurodegenerative disorder or another cognitive impairment, said method comprising:

(a) obtaining endothelium or cells derived from endothelium of said human subject,

(b) culturing endothelial cells therefrom, and

(c) determining whether there is inappropriate senescence and/or defective angiogenesis in at least said endothelial cells which is indicative of vascular dysfunction in said human subject.

2. The method according to Claim 1, wherein said subject is affected by Alzheimer's disease.

5. The method according to Claim 1, wherein there is at least (a) abnormal response by endothelial cells to angiogenic signaling; (b) anoikis, apoptosis, or programmed cell death; (c) mitotic catastrophe; (d) a storage disorder, or (e) a combination thereof.

6. The method according to Claim 1, wherein there is at least (a) defective differentiation of endothelial cells, (b) defective fusion of capillaries or vessels, (c) inappropriate regression of capillaries or vessels, or (d) a combination thereof.

27. A method of assaying for vascular dysfunction in a human subject affected by a neurodegenerative disorder or another cognitive impairment, said method comprising:

(a) obtaining endothelial cells from said human subject,

(b) culturing the endothelial cells to provide cells derived from endothelium, and

(c) determining whether there is inappropriate senescence and/or defective angiogenesis in the cells derived from endothelium;

wherein inappropriate senescence and/or defective angiogenesis in the cells derived from endothelium is indicative of vascular dysfunction.

28. The method according to Claim 27, wherein there is at least abnormal response by cells derived from endothelium to angiogenic signaling.

29. The method according to Claim 27, wherein there is at least anoikis, apoptosis, or programmed cell death of cells derived from endothelium.

30. The method according to Claim 27, wherein there is at least mitotic catastrophe of cells derived from endothelium.

31. The method according to Claim 27, wherein there is at least a storage disorder of cells derived from endothelium.

32. The method according to Claim 27, wherein there is at least (a) defective differentiation of endothelial cells, (b) defective fusion of capillaries or vessels, (c) inappropriate regression of capillaries or vessels, or (d) a combination thereof.

33. A method of assaying for vascular dysfunction in a human subject affected by Alzheimer's disease, said method comprising:

(a) obtaining endothelial cells from said human subject,

(b) culturing the endothelial cells to provide cells derived from endothelium, and

(c) determining whether there is inappropriate senescence and/or defective angiogenesis in the cells derived from endothelium;

wherein inappropriate senescence and/or defective angiogenesis in the cells derived from endothelium is indicative of vascular dysfunction.

34. The method according to Claim 33, wherein there is at least abnormal response by cells derived from endothelium to angiogenic signaling.

35. The method according to Claim 33, wherein there is at least anoikis, apoptosis, or programmed cell death of cells derived from endothelium.

36. The method according to Claim 33, wherein there is at least mitotic catastrophe of cells derived from endothelium.

37. The method according to Claim 33, wherein there is at least a storage disorder of cells derived from endothelium.

38. The method according to Claim 33, wherein there is at least (a) defective differentiation of endothelial cells, (b) defective fusion of capillaries or vessels, (c) inappropriate regression of capillaries or vessels, or (d) a combination thereof.

39. A method of assaying for vascular dysfunction in a human subject affected by Alzheimer's disease, said method comprising determining whether there is defective angiogenesis in at least endothelium of the human subject or cells derived from endothelium of the human subject, wherein defective angiogenesis is indicative of vascular dysfunction.

40. The method according to Claim 39, wherein there is at least (a) defective differentiation of endothelial cells, (b) defective fusion of capillaries or vessels, (c) inappropriate regression of capillaries or vessels, or (d) a combination thereof.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.